Systematic Review and/or Meta-analysis

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Systemic therapy plus HAIC versus systemic therapy for hepatocellular carcinoma: a systematic review and meta-analysis

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Background Hepatic arterial infusion chemotherapy (HAIC) exhibits synergistic anticancer effects with systemic therapy in treating hepatocellular carcinoma (HCC). The approach combining systemic therapy and HAIC is likely to establish a new survival benchmark for advanced HCC. However, related evidence is still lacking.

Method PubMed, Embase, Cochrane Library, and Web of Science were searched from January 1990 to July 2024. The extracted data were pooled using fixed- or random-effects models and expressed as hazard ratios (HRs) or risk ratios (RRs) with corresponding 95% confidence intervals (CIs). Meta-regression, subgroup analysis, prognostic factor analysis, correlation analysis, as well as trial sequential analysis were further conducted.

Result Seventeen trials involving 3070 participants were included. Patients receiving HAIC combined systemic therapy displayed superior overall survival (OS) (HR, 0.52; 95% CI, 0.48–0.58), progression-free survival (PFS) (HR, 0.54; 95% CI, 0.46–0.63), objective response rate (ORR) (RR, 2.20; 95% CI, 1.77–2.72) and disease control rate (RR, 1.21; 95% CI, 1.14–1.29) over systemic therapy. Combining HAIC resulted in higher incidences of grade ≥3 manageable adverse events. Subgroup analyses showed that HAIC could bring significant survival improvement for almost all specific populations; however, patients without portal vein tumor thrombosis might not benefit from it (HR, 0.74; 95% CI, 0.53–1.03). Prognostic factor analyses found extra HAIC was a protective factor for both OS (HR, 0.42; 95% CI, 0.34–0.51) and PFS (HR, 0.44; 95% CI, 0.36–0.53). Correlation analyses demonstrated a robust association between ORR and OS when applying systemic therapy with HAIC (*P*-value = 0.031). In addition, trial sequential analyses visually showed the present data were compelling to draw reliable conclusions.

Conclusion With manageable toxicity, integrating HAIC with systemic therapy could bring favorable survival benefits for HCC patients. Further evidence is necessary to standardize the integration of HAIC with first-line systemic therapy.

Keywords: antineoplastic protocols, hepatocellular carcinoma, immunotherapy, intra-arterial infusion

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide, with its incidence ranking sixth among malignancies[1]. Most HCC patients were diagnosed at intermediate to advanced stages (stages B–C of the Barcelona Clinic Liver Cancer system), which were ineligible for curative regimens including surgery, ablation, or transplantation[2]. Given their significant anti-tumor efficacy, molecular and immune therapy have become the mainstream treatment of unresectable HCC in the past two decades[3,4]. Nevertheless, the 5-year survival rate of advanced HCC

HIGHLIGHTS

- This meta-analysis first thoroughly elucidated the integration of HAIC to systemic therapies.
- With manageable toxicity, systemic therapy plus HAIC is likely to set a new benchmark for HCC patients' survival.
- This amalgamation of therapies effectively converted ORR to survival, which was superior to HAIC monotherapy or systemic therapy only.
- Patients without PVTT might not benefit from the integrated HAIC.
- From the aspect of data adequacy, trial sequential analysis illustrated the stability of our conclusions.

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receiving nivolumab remains suboptimal, ranging from 14% to 28%[5]. Hence, powerful therapeutic strategies are necessary for prolonging the survival of HCC patients.

As a potent traditional locoregional treatment, hepatic arterial infusion chemotherapy (HAIC) delivers anticancer chemical agents directly to intrahepatic tumor sites, and has been demonstrated to be effective and safe[6]. Recent studies revealed that HAIC could exert a synergistic effect when combined with tyrosine kinase inhibitors (TKIs) or/and immune checkpoint inhibitors (ICIs)[7,8]. HAIC has the advantage of rapidly debulking tumor by effectively killing cancer cells, which not only weakens tumor burden for systemic therapy, but also releases tumor antigens through inducing immunogenic cell death, triggering powerful immune activation against the neoplasms[6,9]. Several trials further revealed the benefit of integrating HAIC into systemic therapy for advanced HCC patients, even in those with tricky issues such as main portal vein tumor thrombosis (PVTT) and extrahepatic metastases[10–12]. In a phase III randomized study of participants with PVTT, the overall survival (OS) was significantly improved in HAIC plus sorafenib group compared to the single sorafenib group[8]. Besides, a retrospective study included patients with extrahepatic metastasis implied that the better control of intrahepatic lesions attributed to the distinctly prolonged OS in patients receiving HAIC plus lenvatinib plus programmed death-1 (PD-1) inhibitors compared with those applying lenvatinib plus PD-1 inhibitors[12]. Hence, the integration of HAIC to systemic therapy is likely to set a new benchmark for the OS of advanced HCC.

In this study, we included studies evaluating the feasibility of integrating HAIC to systemic therapy and pooled the results, including OS, progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs) incidence. Furthermore, we conducted detailed subgroup analyses and prognostic factor analyses to assist the clinical practice of adding HAIC to systemic therapy.

Methods

This meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement[13]. We assessed the methodological quality through the AMSTAR guidelines[14]. It was registered in the PROSPERO international prospective registry for systematic reviews.

Search strategy and inclusion criteria

We extensively searched PubMed, Embase, The Cochrane Library, and Web of Science for published articles from 1 January 1990 to 5 July 2024. Search terms were derived from Medical Subject Headings and free-text keywords, including "hepatocellular carcinoma," "hepatic arterial infusion," "tyrosine kinase inhibitor," and "immune checkpoint inhibitor." The full search strategy was recorded in Supplementary Table 1 (Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). The reference lists of related studies were manually searched to identify potentially related articles.

Qualified studies were in accordance with the following criteria: (i) studies investigating the comparison between groups using identical systemic therapies with or without HAIC treatment in patients with advanced HCC, and certain studies in which TACE was applied in both groups were included; (ii) studies reporting one or more outcomes, including OS, PFS, ORR, DCR, and AEs; (iii) cohort or case-control study or randomized controlled trial (RCT). The exclusion criteria were as follows: (i) Case reports, editorials, comments, reviews, and conference abstracts; (ii) studies with insufficient data for outcome assessment; (iii) studies with overlapping data due to the same research population.

Data extraction and quality assessment

Available data from included studies were independently extracted by two reviewers (DHL and HL) with a standardized form. Discrepancies were resolved through consensus discussion between the reviewers. The selected data included study characteristics (first author, publication year, country, study design, number of patients, median follow-up time, reported outcomes), patient characteristics (age, gender, tumor stage, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), maximum tumor size, tumor number, hepatitis B virus (HBV) or hepatitis C virus (HCV) infection status, Child-Pugh score, α-fetoprotein (AFP) level, portal vein tumor thrombus (PVTT), extrahepatic spread, treatment approaches (including dosage, duration and management strategies), and outcomes (OS, PFS, ORR, DCR, grade ≥3 AEs). Data of ORR and DCR were extracted according to the modified Response Evaluation Criteria in Solid Tumors[15].

The Cochrane risk of bias tool was applied to assess the methodological quality of RCTs[16]. The modified Newcastle–Ottawa Scale (NOS) was used to evaluate the methodological quality of observational studies[17]. Studies with NOS score ≥6 were deemed high quality.

Statistical analysis

Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were calculated for the effect measure of OS and PFS. Risk ratios (RRs) with corresponding 95% CIs were used to evaluate tumor response rates and adverse effects. Data were pooled using the fixed- (I^2 < 50%) or random-effects models (I^2 ≥ 50%) on the basis of the degree of heterogeneity among the included studies, which was tested mainly through the I^2 statistic[18,19]. I^2 values of 25%, 50%, and 75% were interpreted as indicating low, moderate, and high heterogeneity, respectively[20]. Publication bias was identified through funnel plots and quantified by Egger's regression model[21]. Sensitivity analysis was conducted when I^2 > 50% to sequentially examine each study to find potential sources of heterogeneity. A two-sided P-value <0.05 was defined as statistical significance. All analyses and visualizations were processed using R software version 4.4.0 (R package: meta[22]; forestploter[23]).

Meta-regression analysis, subgroup analysis, prognostic factor analysis, and correlation analysis

Meta-regression analysis was performed to detect the potential factors leading to marked heterogeneity among studies. We set platinum-based agents (oxaliplatin/cisplatin), type of systemic therapy (targeted therapy alone/targeted-plus-immunotherapy), and study design (RCT/retrospective cohort) as independent variables (x) and the outcome measures served as dependent variables (y). We conducted multiple subgroup analyses according to study characteristics, patient baseline information, tumor

stage, and treatment approaches. Pooled HRs from univariate or multivariate analysis were obtained through included trials to identify potential risk and protective factors for OS and PFS. Correlations of ORR and survival outcomes (OS/PFS) were calculated by Spearman's correlation analysis conducted in R software 4.4.0.

Trial sequential analysis

Trial sequential analysis (TSA) is a statistical methodology used to calculate the required information size and form trial sequential monitoring boundaries[24]. The selection of random- or fixed-effects model was determined by the absence or presence of marked heterogeneity (I^2 > 50%) in our meta-analysis. To control both type I and type II errors, an overall 5% risk of type I error rate (α = 0.05) with 80% statistical power (β = 0.20) was predefined to establish thresholds for both statistical significance and futility boundaries[25]. The relative risk reduction (RRR) was set according to the pooled effect estimates from the primary analysis. In our investigation, the TSA was conducted using TSA software (version 0.9.5.10 beta).

Result

Study selection and characteristics

After the initial search, 1743 literatures were retrieved. Titles and abstracts were screened for 1047 studies after excluding duplicated studies, and the full-text screening was conducted in 52 studies.

The process of selection is shown in Figure 1. The final analysis included 17 studies (4 RCTs and 13 retrospective cohorts) comprising 3070 patients[7,8,10–12,26–37], with median follow-up durations ranging from 9.7 to 25.0 months. For

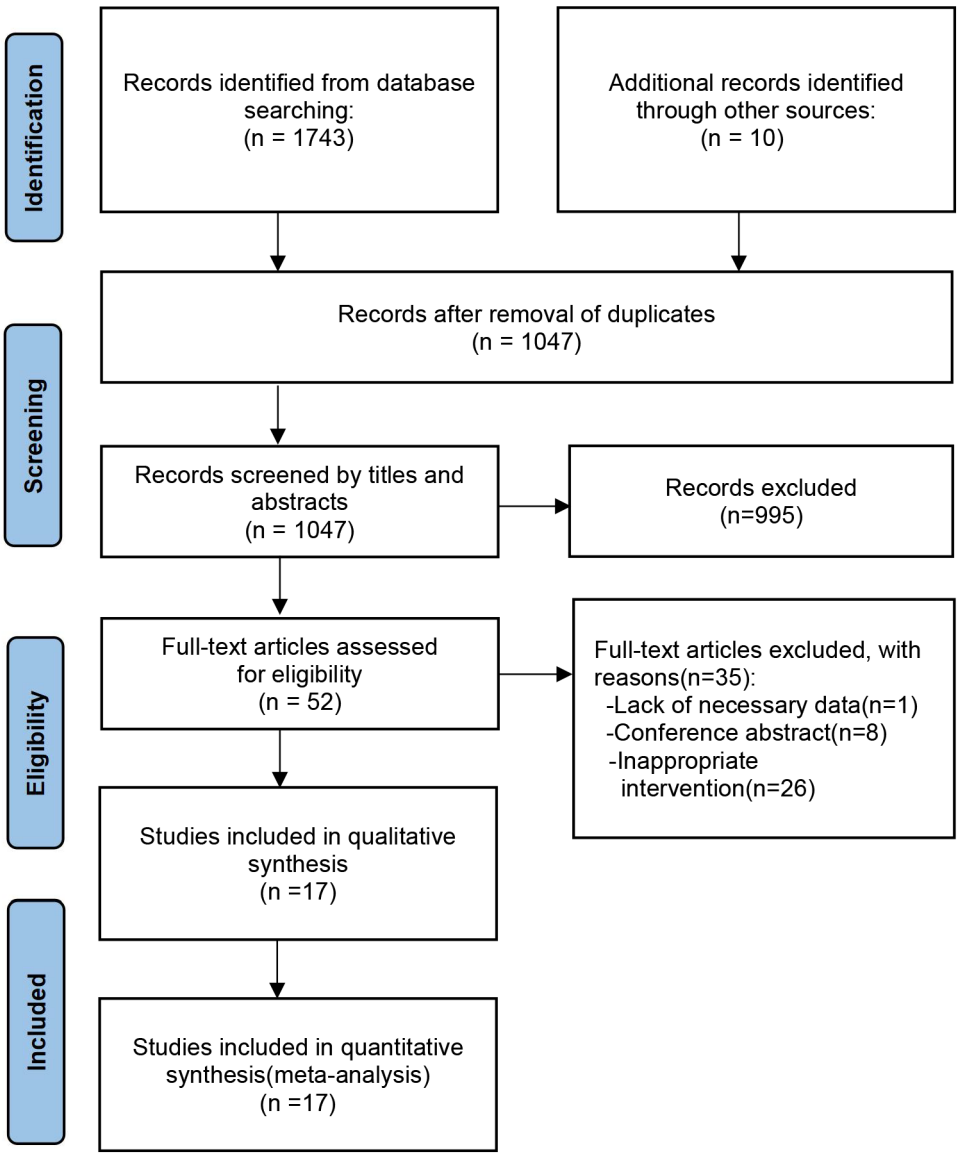

Figure 1. Flowchart of the study selection process.

treatment approaches, oxaliplatin-based HAIC treatment was employed for 14 studies[7,8,10–12,26–34] of which FOLFOX (oxaliplatin, fluorouracil, and leucovorin) or modified FOLFOX regimens were applied in 13 studies[7,8,10–12,26–33]. The cisplatin-based HAIC was used in the remaining three studies[35–37]. Mono-TKIs were used in seven trials[8,26,27,34–37], while TKIs plus ICIs were used in 10 studies[7,10–12,28–33]. In total, there were three combination strategies, including cisplatin-based HAIC plus TKIs used in three studies[35–37], oxaliplatin-based HAIC plus TKIs in four studies[8,26,27,34] or plus TKIs and ICIs in 10 trials[7,10–12,28–33]. The TKIs mainly included lenvatinib, sorafenib, and apatinib. The ICIs comprised sintilimab, camrelizumab, and tislelizumab, nivolumab, toripalimab, etc. In addition, TACE was used in both groups[26,31]. More details of study characteristics, such as therapeutic regimens, patient number, the distribution of age and gender, as well as the available data for analysis of included studies are displayed in Table 1. Patient baseline information and tumor characteristics, including hepatitis etiology, cirrhosis status, liver function, tumor number, tumor size, PVTT status, and extrahepatic metastasis status, are summarized in Supplementary Table 2 (Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). Detailed treatment protocols and management strategies are collected in Supplementary Table 3 (Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). The methodological quality assessment for four RCTs is reported in Supplementary Table 4 (Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20)[8,27,35,37]. Given the invasive nature of HAIC, none of the RCTs adhered to the blinding principles. Besides, two RCTs followed the blinding of the outcome assessment[27,37]. According to the modified NOS, all observational studies were assessed to be of high quality (≥6 stars)[7,10–12,26,28–34,36], and the details are listed in Supplementary Table 5 (Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). Overall, the methodological quality of the included articles was satisfactory.

Overall survival

All included studies (N = 17) reported OS[7,8,10–12,26–37], and the pooled results showed that HAIC combined with systemic therapy was superior to systemic therapy alone (HR, 0.52; 95% CI, 0.48–0.58), with moderate heterogeneity (I^2 = 51%) (Fig. 2A). Patients with solitary tumor (HR, 0.24; 95% CI, 0.16–0.36) had better outcomes than those with multiple lesions (HR, 0.50; 95% CI, 0.42–0.61). But no notable difference was found in patients without PVTT between these two groups (HR, 0.74; 95% CI, 0.53–1.03; P-value = 0.07) (Fig. 3A). More detailed information, including available studies and heterogeneity, is demonstrated in Supplementary Figure 1A–O (Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20).

Meta-regression analysis elucidated that platinum-based agent (oxaliplatin/cisplatin) had a significant impact on OS (P-value <0.0001), whereas neither the type of systemic therapy nor study design showed a significant association (P-value = 0.20 and P-value = 0.46, respectively) (Supplementary Table 6, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). Furthermore, subgroup analyses revealed no statistically significant differences for these three associations (P-value = 0.06, P-value = 0.94, and P-value = 0.98, respectively) (Supplementary Figure 3A–C, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). In addition, patients using oxaliplatin-based HAIC combined with TKIs plus ICIs (HR, 0.52; 95% CI, 0.47–0.59) or TKIs alone (HR, 0.41; 95% CI, 0.34–0.50) achieved notably prolonged OS compared to those not receiving HAIC. However, cisplatin-based HAIC combined with TKIs did not improve OS significantly compared to TKIs alone (HR, 0.73; 95% CI, 0.49–1.10) (Supplementary Figure 3D, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). Sensitivity analysis suggested that the study by Kudo *et al*[35] significantly influenced the pooled HR of OS (Supplementary Figure 4A, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). Furthermore, no biased reporting for OS was found through funnel plot or Egger's test (P-value = 0.2474) (Supplementary Figure 5A, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20).

Progression-free survival

Pooled analyses of PFS were available in 14 studies[7,8,10–12,27–30,32–35,37]. HAIC-combined group yielded a notably better PFS than non-HAIC group (HR, 0.54; 95% CI, 0.46–0.63), with moderate degree of heterogeneity (I^2 = 65%) (Fig. 2B). However, no significant difference was observed between the two groups in patients with liver function as Child-Pugh B grade (HR, 0.64; 95% CI, 0.38–1.08; P-value = 0.10) (Fig. 3B). The Supplementary Figure 2A–L (Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20) illustrated the corresponding studies and heterogeneity.

Meta-regression analysis revealed that both platinum agents and study design impacted PFS significantly (P-value <0.0001 and P-value = 0.03, respectively), but the type of systemic therapy had no significant impact (P-value = 0.79) (Supplementary Table 6, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). Additionally, oxaliplatin-based HAIC was associated with better PFS than cisplatin-based HAIC (P-value <0.01) (Supplementary Figure 3E, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). No statistical difference was observed between the single targeted therapy group and the targeted-plus-immunotherapy group (P-value = 0.52) (Supplementary Figure 3F, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20), or between RCTs and retrospective cohorts (P-value = 0.55) (Supplementary Figure 3G, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). Furthermore, patients receiving integrated HAIC obtained notably improved PFS than those without, regardless of different therapeutic combination regimens. However, a significant difference existed between oxaliplatin-based HAIC combined with TKIs (HR, 0.37; 95% CI, 0.25–0.54) and cisplatin-based HAIC (HR, 0.76; 95% CI, 0.60–0.96) (P-value < 0.01) (Supplementary Figure 3H, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). Sensitivity analysis confirmed the stability of the pooled results (Supplementary Figure 4B, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). No publication bias existed according to the

Table 1

Characteristics of included studies.

Study (author, year)	Treatment regimen (HAIC + systemic therapy/systemic therapy alone)	Design (retrospective/ RCT)	Patient numbers	Sex (male/female)	Age (year)	Median follow-up (months)	Evaluated outcomes
Mei *et al*[27]	HAIC + LEN + PD-1 inhibitor	Retrospective	45	38/7 (84.4%/15.6%)	49.1 ± 10.6	15.1	OS, PFS, ORR, DCR, grade ≥3 AE
	LEN + PD-1 inhibitor		25	18/7 (72.0%/28.0%)	50.1 ± 12.3		
Chen *et al*[29]	HAIC + LEN + Pembrolizumab	Retrospective	84	72/12 (84.5%/ 15.5%)	52 (42–67)	18.6	OS, PFS, ORR, DCR
	LEN + Pembrolizumab		86	71/15 (82.6%/ 17.4%)	53 (43–69)		
Fu *et al*[7]	HAIC + LEN + PD-1 inhibitor	Retrospective	89	83/6 (93.3%/6.7%)	51.9 ± 10.5	15.8	OS, PFS, ORR, DCR, grade ≥3 AE
	LEN + PD-1 inhibitor		53	50/3 (94.3%/5.7%)	53.5 ± 10.5	22	
Guan *et al*[12]	HAIC + LEN + PD-1 inhibitor	Retrospective	127	107/20 (84.25%/ 15.75%)	51.90 ± 10.88	16.5	OS, PFS, ORR, DCR, grade ≥3 AE
	LEN + PD-1 inhibitor		103	94/9 (91.26%/ 8.74%)	54.01 ± 11. 54	19.5	
Li *et al*[11]	HAIC + Rivoceranib + Camrelizumab	Retrospective	292	267/25 (91.4%/ 8.6%)	51.0 (43.0–58.0)	19.7	OS, PFS, ORR, DCR, grade ≥3 AE
	Rivoceranib + Camrelizumab		119	111/8 (93.3%/6.7%)	53.0 (45.0–58.0)		
Diao *et al*[10]	HAIC + LEN + PD-1 inhibitor	Retrospective	58	49/9 (84.5%/15.5%)	≤50/ > 50: 16/ 52	22.1	OS, PFS, ORR, DCR, grade ≥3 AE
	LEN + PD-1 inhibitor		63	50/13 (79.4%/ 20.6%)	≤50/ > 50: 5/27		
Chang *et al*[30]	HAIC + LEN + PD-1 inhibitor	Retrospective	103	91/12 (88.3%/ 11.7%)	52.0 ± 8.82	16.3	OS, PFS, ORR, DCR, grade ≥3 AE
	LEN + PD-1 inhibitor		61	57/4 (93.4%/6.6%)	56.0 ± 7.88	24.1	
Cai *et al*[23]	HAIC + LEN + D-TACE	Retrospective	105	97/8 (92.4%/7.6%)	52.8 ± 11.4	17.0 ± 6.4	OS, ORR, DCR, grade ≥3 AE
	LEN + D-TACE		100	89/11 (89.0%/ 11.0%)	53.0 ± 10.9	13.2 ± 5.7	
Huang *et al*[25]	HAIC + TACE + TKI + PD-1 inhibitor	Retrospective	63	57/6 (90.5%/9.5%)	≤60/ > 60: 43/20	11	OS, ORR, DCR
	TACE + TKI + PD-1 inhibitor		60	52/8 (86.7%/13.3%)	≤60/ > 60: 34/26		
Zuo *et al*[26]	HAIC + Apatinib + Camrelizumab	Retrospective	207	185/22 (89.37%/ 10.63%)	≤65/ > 60: 190/17	22.8	OS, PFS, ORR, DCR, grade ≥3 AE
	Apatinib + Camrelizumab		209	188/21 (89.95%/ 10.04%)	≤65/ > 60: 181/28	24.5	
Wang *et al*[26]	HAIC + TKI + PD-1 inhibitor	Retrospective	99	81/18 (81.8%/ 18.2%)	56.40 ± 8.70	NA	OS, PFS, ORR, DCR, grade ≥3 AE
	TKI + PD-1 inhibitor		95	78/17 (82.1%/ 17.9%)	57.11 ± 8.60	NA	
Ikeda *et al*[34]	HAIC + SOR	RCT	65	56/9 (86.2%/13.8%)	66 (25-79)	NA	OS, PFS, ORR, DCR, grade ≥3 AE
	SOR		41	32/9 (78.0%/22.0%)	64 (42-78)	NA	
Ikuta *et al*[33]	HAIC + SOR	Retrospective	26	20/6 (76.9%/23.1%)	72.4 ± 8.9	9.7 (1.2–58.8)	OS, ORR, DCR, grade ≥3 AE
	SOR		72	61/11 (84.7%/ 15.3%)	69.0 ± 9.9		
Kudo *et al*[32]	HAIC + SOR	RCT	102	89/13 (87.3%/ 12.7%)	66.7 ± 10.2	NA	OS, PFS, ORR, DCR, grade ≥3 AE
	SOR		103	88/15 (85.4%/ 14.6%)	68.1 ± 9.1	NA	
Zhao *et al*[31]	HAIC + SOR	Retrospective	46	41/5 (89.1%/10.9%)	≤50/ > 50: 27/19	NA	OS, PFS, grade ≥3 AE
	SOR		58	54/4 (93.1%/6.9%)	≤50/ > 50: 30/28	NA	
He *et al*[8]	HAIC + SOR	RCT	125	111/14 (88.8%/ 11.2%)	49 (41–55)	NA	OS, PFS, ORR, DCR, grade ≥3 AE
	SOR		122	112/10 (91.8%/ 8.2%)	49 (40–56)	NA	
Zheng *et al*[24]	HAIC + SOR	RCT	32	30/2 (93.8%/6.2%)	56 ± 11	25.0 (20.7, 29.3)	OS, PFS, ORR, DCR, grade≥3 AE
	SOR		32	31/1 (96.9%/3.1%)	55 ± 10	16.4 (10.0, 22.8)	

AEs, adverse events; DCR, disease control rate; HCC, hepatocellular carcinoma; HAIC, hepatic arterial infusion chemotherapy; LEN, lenvatinib; NA, not available; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PFS, progression-free survival; RCT, randomized controlled trial; SOR, sorafenib, TACE; transarterial chemoembolization.

funnel plot or Egger's test (*P*-value = 0.2635) (Supplementary Figure 5B, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20).

Objective response rate

Data of ORR were reported in 16 studies[7,8,10–12,26–33,35–37]. The HAIC-combined group reached an ORR of 54.86%, significantly higher than 25.19% observed in the non-HAIC group (RR, 2.20; 95% CI, 1.77–2.72) with moderate heterogeneity (I^2 = 65%) (Fig. 2C).

Meta-regression analysis found that the study design notably affected ORR (*P*-value = 0.01) (Supplementary Table 6, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20), and it was more evident in the RCTs compared to retrospective cohorts (*P*-value = 0.04) (Supplementary Figure 3K, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20), whereas the type of systemic therapy and platinum agents failed to show a notable effect for the heterogeneity (*P*-value = 0.60 and *P*-value = 0.11, respectively) (Supplementary Table 6, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). Additionally, no statistical differences were observed between the subgroups divided by these two factors (*P*-value = 0.51 and *P*-value = 0.07, respectively) (Supplementary Figure 3I and J, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). Consistently, patients receiving HAIC demonstrated significantly improved ORR compared to those without HAIC across all three combination regimens, with no statistical differences among the regimens (Supplementary Figure 3L, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). Sensitivity analysis confirmed the robustness of the results (Supplementary Figure 4C, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20).

Disease control rate

Data concerning DCR were available in 15 studies[7,8,10–12,26–33,35,36]. The DCR was 86.90% in the HAIC-combined systemic therapy group and 71.00% in the systemic therapy-alone group. The integration of HAIC significantly enhanced the DCR (RR, 1.21; 95% CI, 1.14–1.29) with moderate heterogeneity (I^2 = 55%) (Fig. 2D).

Meta-regression analysis indicated that platinum-based agents (oxaliplatin/cisplatin), the type of systemic therapy, or study design had no significant impact on DCR (*P*-value = 0.12, *P*-value = 0.58, *P*-value = 0.47, respectively) (Supplementary Table 6, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). No significant differences were observed in subgroup analysis based on these three variables (*P*-value = 0.62, *P*-value = 0.43, and *P*-value = 0.43, respectively) (Supplementary Figure 3M–O, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). Moreover, DCR in patients receiving cisplatin-based HAIC plus TKIs was not notably enhanced compared to those without HAIC (HR, 1.14; 95% CI, 0.87–1.50). No significant differences were observed among the three combination regimens (Supplementary Figure 3P, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20). Sensitivity analysis suggested no single study significantly affected DCR (Supplementary Figure 4D, Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20).

Adverse events

Grade ≥3 AEs of these two treatment approaches were reported in 15 studies[7,8,10–12,26–30,33–37]. Overall, the incidence of grade ≥3 AEs was 7.20% in the HAIC-combined group and 4.58% in the non-HAIC group. Among them, abdominal pain, fever, hypertension, nausea/vomiting, decreased leukocyte, decreased platelet, diarrhea, elevated ALT, and elevated AST were more frequent in the HAIC-combined group. Details of grade ≥3 AEs are summarized in Supplementary Figure 6 (Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20).

Prognostic factor analysis of OS and PFS

Prognostic factor analyses of OS and PFS were performed using the HRs of Cox regression. Results regarding OS indicated that integrated HAIC treatment, liver function of Child-Pugh A grade, a lower ECOG-PS score were protective factors, whereas the presence of main portal vein invasion (tumor thrombus in first-order branches or in the main trunk) and extrahepatic metastases were risk factors (Fig. 4A). As for PFS, integrated HAIC was potentially a protective factor, while AFP >400 ng/ml was considered a risk factor (Fig. 4B). Information regarding included trials and heterogeneity is displayed in Supplementary Figure 7A– N (Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20) and Supplementary Figure 8A–K (Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E20) in detail.

Correlation analysis between objective response rates and survival outcomes

Correlation analysis was performed to investigate the association between ORR and survival outcomes, which was essential to explain the confusion between high ORR and relatively suboptimal survival observed with HAIC monotherapy or systemic therapy alone. We found a significantly negative association (indicator of high ORR and prolonged OS) between ORR_{RR} and OS_{HR} (R = – 0.54, P = 0.031) and an absence of robust association between ORR_{RR} and PFS_{HR} (R = – 0.52, P = 0.069) (Fig. 5A and B). Furthermore, considering the wider application of FOLFOX regimens, we analyzed data from studies using HAIC with FOLFOX regimens to conduct correlation analysis, revealing strong associations between ORR_{RR} and OS_{HR} (R = –0.79, *P*-value = 0.0013), as well as ORR_{RR} and PFS_{HR} (R = –0.81, *P*-value = 0.0027) (Fig. 5C and D).

TSA for ORR and DCR

TSA was performed to assess the stability of conclusion through evaluating the adequacy of data for pooling ORR/DCR. Based on the aforementioned outcomes, RRR was set at 30% for ORR and 15% for DCR. The required information sizes were calculated as 2633 patients for ORR and 1469 patients for DCR. The cumulative Z curves intersected both the trial sequential monitoring boundaries and the RIS lines, confirming the reliability of the meta-analysis results that supported the benefit of the integration of HAIC into systemic therapy, and the present data were sufficient to establish a clinically meaningful difference in ORR and DCR, thus more trials may be unnecessary to validate these outcomes (Fig. 6A and B).

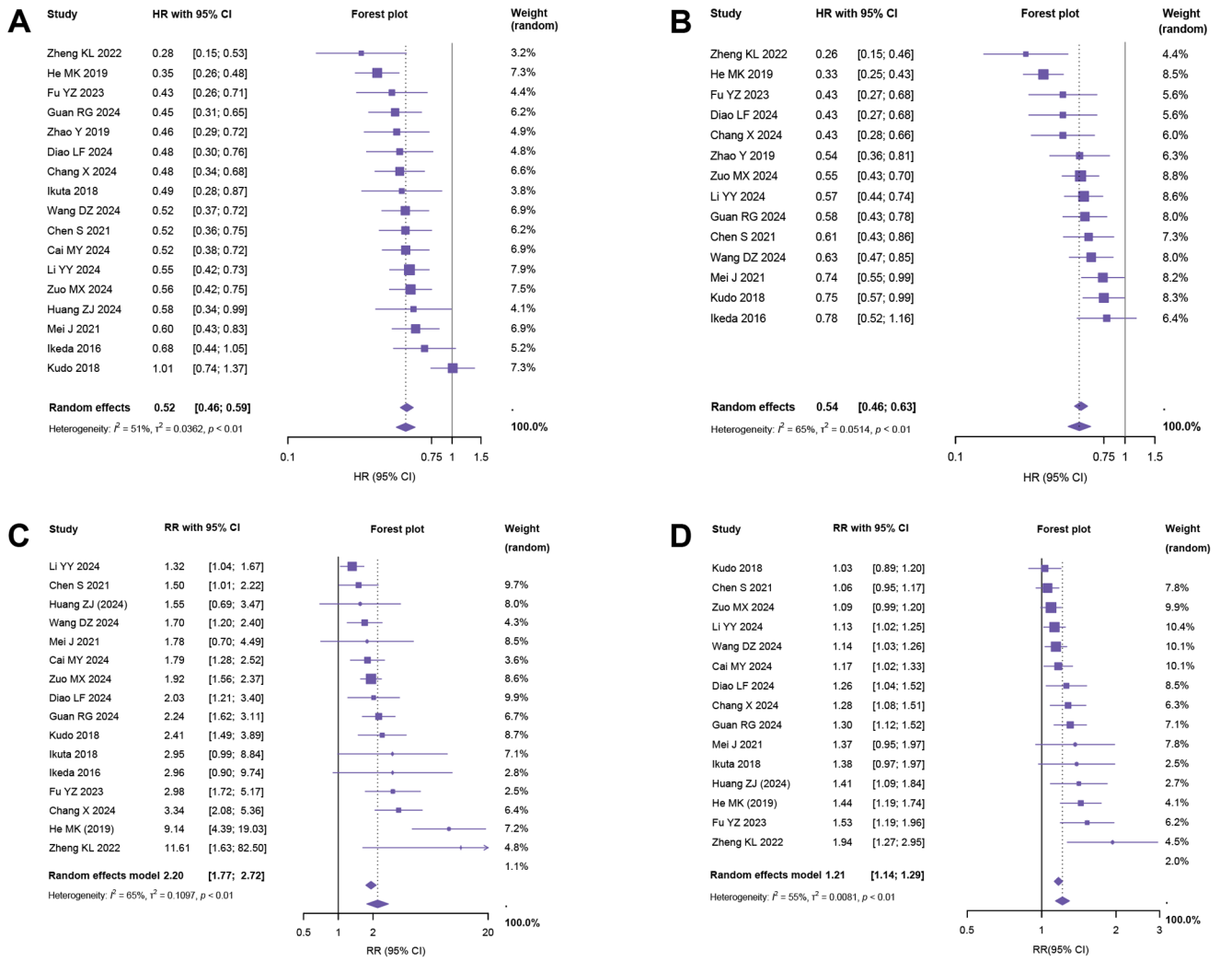

Figure 2. Systemic therapy plus HAIC versus systemic therapy for hepatocellular carcinoma (HCC). (A) overall survival (OS); (B) progression-free survival (PFS); (C) objective response rate (ORR); (D) disease control rate (DCR).

Discussion

Integrating HAIC to systemic therapy is likely to set a new survival benchmark for advanced HCC. Related evidence is lacking for clinical practice. To our knowledge, this is the first meta-analysis extensively investigating the efficacy and safety of the additional HAIC treatment for systemic therapies in patients with advanced HCC. The favorable survival outcomes and considerable radiological response rates along with manageable AEs manifested in our study are encouraging. Moreover, meta-regression analyses and subgroup analyses supplied preliminary references in selecting optional combination regimens and populations. The prognostic factor analyses helped to identify the influential factors for HAIC-based systemic regimens. Furthermore, correlation analyses revealed a strong association between ORR and OS in patients receiving additional HAIC for the first time, particularly those with FOLFOX regimens, which differed from previous results focusing on HAIC monotherapy[38], providing a potential alternative endpoint. Finally, TSA demonstrated that available data for calculating ORR/DCR are enough to draw present conclusions.

An important theoretical basis for integrating HAIC to systemic therapy was the synergistic anticancer abilities of HAIC. It was reported that HAIC could effectively promote tumor shrinkage through direct administration of high doses of potent chemical drugs, which not only accounted for the eradication of micro-metastases that were difficult to identify with imaging, but could be effective in treating PVTT because of its blood supply from hepatic arteries[39,40]. As mentioned above, HAIC exerted a potent synergistic effect when combined with TKIs and/or ICIs. First, oxaliplatin as a component of FOLFOX regimens, could augment antigenicity and promote infiltration of mature dendritic cells and $CD8^+$T cells in the tumor microenvironment by inducing immunogenic cell death of cancer cells, playing a crucial role in immunomodulation and reconstruction of the tumor microenvironment[41–43]. Moreover, TKIs such as sorafenib and lenvatinib, help overcome the resistance of tumor cells to chemical agents and ICIs through facilitating vascular normalization, resulting in the disruption of the hypoxic tumor microenvironment[44,45]. Therefore, positive effect of HAIC plus TKIs on tumor microenvironment has the potential of transforming cold tumors into hot ones, restoring

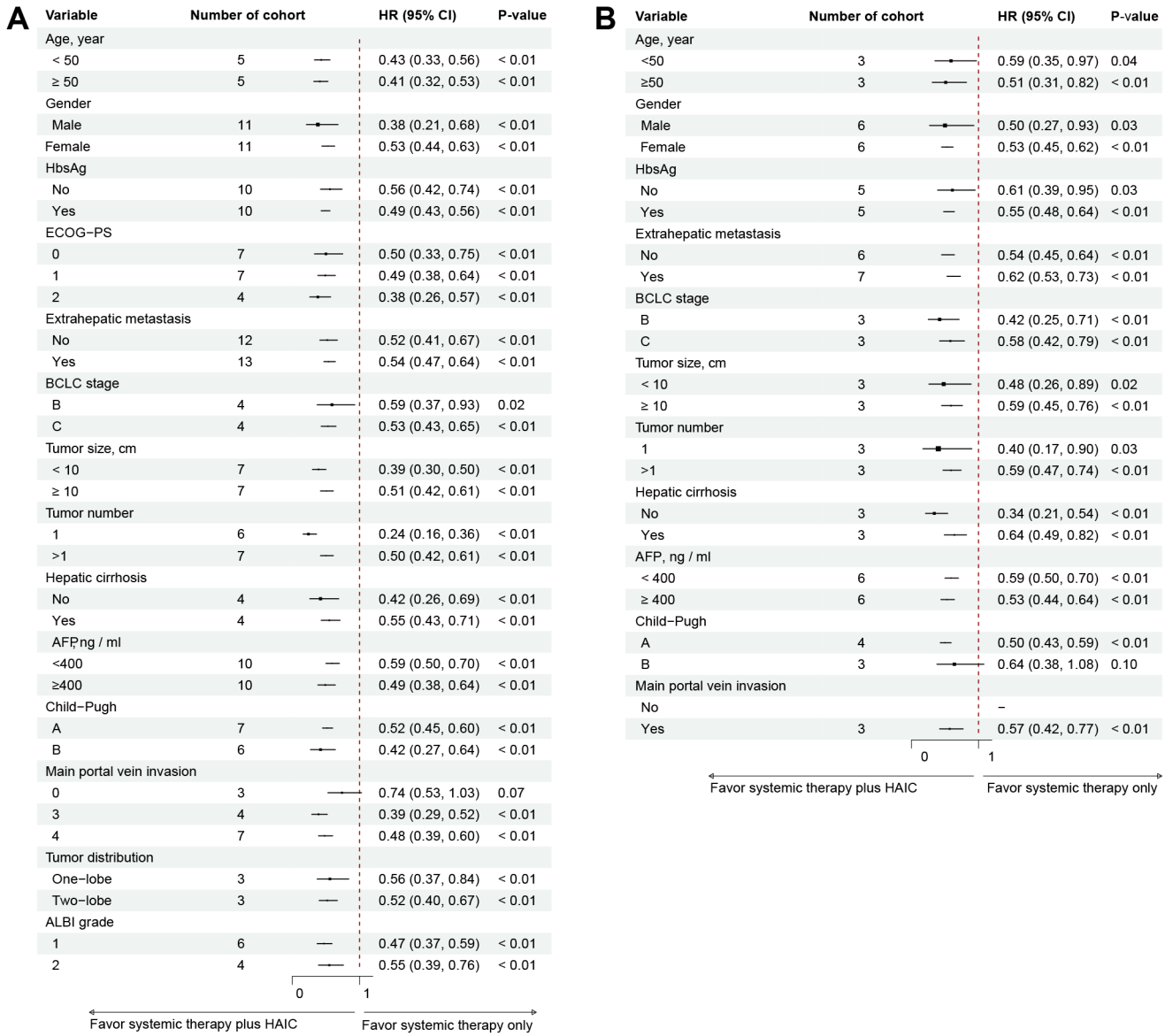

Figure 3. Subgroup analyses of included studies. (A) Overall survival (OS); (B) progression-free survival (PFS).

the immune surveillance, and thus enhancing the efficacy of PD-1 inhibitors. Meanwhile, the application of systemic therapy to treatment intervals of HAIC helped maintain or increase tumor response rates and reduce the dosage or frequency of chemical drugs. Besides, conventional TACE (cTACE) as a cornerstone intra-arterial intervention, played a vital role for HCC. Recently, a multi-center, prospective study demonstrated survival benefits and enhanced tumor response rates with cTACE combined with systemic agents[46]. However, emerging retrospective evidence suggests that compared to TACE, HAIC could offer comparable or even superior efficacy for patients receiving targeted therapy plus immunotherapy, even for those with more advanced tumor stages[47,48]. This divergence could be attributed to HAIC's pharmacokinetic advantage, as it continuously delivers high concentrations of chemotherapeutic agents to the tumor sites, and thus potentiating synergistic effects with systemic therapies. In contrast, cTACE-induced transient ischemia may inadvertently promote pro-angiogenic factors, potentially accelerating tumor recurrence[49,50]. Therefore, to better demonstrate the efficacy improvement from integrated HAIC, we designed this study specifically focusing on this modality. Furthermore, concurrent application of cTACE and HAIC with systemic therapies is being increasingly explored clinically with the aim of leveraging their potential complementary roles in treating advanced HCC[50]. Therefore, it is urgently required to optimize their combination strategy and validate their efficacy and safety profiles in future research.

The crossing of effective phases may also be a reason for integrating HAIC to systemic therapy. A vital reason impeding HAIC from becoming the first-line therapy of HCC is the drug resistance, which makes the initial high tumor response fail to translate into survival benefit. A recent study comparing HAIC

Independent factor	Number of cohort	Forest plot	HR (95% CI)	P-value
Overall Survival				
Age (year) (< 50 vs ≥50)	3		1.07 (0.77, 1.48)	0.68
Gender (male vs female)	8		1.07 (0.85, 1.36)	0.56
Hepatitis B (no vs yes)	7		0.94 (0.75, 1.19)	0.62
AFP (ng/ml) (< 400 vs ≥400)	8		0.83 (0.62, 1.10)	0.19
Liver cirrhosis (no vs yes)	5		0.83 (0.63, 1.10)	0.20
Child−Pugh (A vs B)	8		0.49 (0.32, 0.75)	< 0.01
BCLC (C vs B)	6		1.17 (0.93, 1.46)	0.17
Tumor size (cm)(< 10 vs ≥10)	4		1.00 (1.00, 1.00)	0.97
Tumor number (multiple vs solitary)	4		1.45 (0.82, 2.59)	0.20
Main portal vein invision (yes vs no)	7		1.30 (1.08, 1.56)	0.01
Extrahepatic metastases (yes vs no)	8		1.40 (1.05, 1.88)	0.02
Integrated HAIC (yes vs no)	7		0.42 (0.34, 0.51)	< 0.01
ECOG−PS (0 vs 1)	4		0.79 (0.63, 0.99)	0.04
Progression Free Survival				
Age (year) (< 50 vs ≥50)	3		0.89 (0.66, 1.19)	0.43
Gender (male vs female)	5		1.28 (0.98, 1.67)	0.07
Hepatitis B (no vs yes)	5		1.06 (0.83, 1.36)	0.64
AFP (ng/ml) (< 400 vs ≥400)	5		0.62 (0.39, 0.99)	0.04
Liver cirrhosis (no vs yes)	4		0.87 (0.64, 1.18)	0.36
Child−Pugh (A vs B)	5		0.65 (0.39, 1.08)	0.09
BCLC (C vs B)	4		1.05 (0.78, 1.42)	0.73
Main portal vein invision (yes vs no)	5		1.02 (0.84, 1.24)	0.82
Extrahepatic metastases (yes vs no)	5		1.36 (0.96, 1.93)	0.08
Integrated HAIC (yes vs no)	5		0.44 (0.36, 0.53)	< 0.01

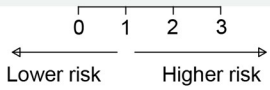

Figure 4. Prognostic factors analysis for overall survival (OS) and progression-free survival (PFS).

monotherapy and sorafenib reported that the initial high tumor response rates of HAIC were not bound to convert into survival benefits, and the deficiency in continuous tumor control might drive the phenomenon[38]. Conversely, our correlation analysis revealed that ORR was notably associated with OS, especially when combining HAIC with FOLFOX regimens. The opposite findings supported the superiority of integrating HAIC into systemic therapy. During HAIC plus systemic therapy, HAIC induced a high tumor response at the initial stage; subsequently, slower-acting systemic therapy became the main force to enhance tumor response. This approach of HAIC plus systemic therapy could not only control the tumor rapidly (mainly induced by HAIC), but also facilitate sustained tumor response (mainly induced by systemic therapy), and ultimately bring greater survival benefits to HCC patients. Additionally, ORR may serve as a surrogate endpoint for future studies focusing on HAIC-combined systemic therapy.

The HAIC plus systemic therapy also has great potential in preoperative therapy, including neoadjuvant therapy and conversion therapy[51]. It is noteworthy that increased antitumor activity may bring more chances to curative operations for patients with advanced HCC. In the study by Zuo *et al*[28], the ORR in HAIC-combined group was significantly higher than that in the non-HAIC group. Furthermore, patients who received curative therapies in HAIC combined with apatinib plus camrelizumab group reached 26.2%, distinctly higher than 7.7% of apatinib plus camrelizumab group[28]. Similarly, Fu *et al*[7] reported that the ORR exhibited in HAIC combined with lenvatinib plus PD-1 inhibitor group was threefold higher than that in lenvatinib plus PD-1 inhibitor group. Intriguingly, four patients receiving hepatectomy had a complete response both in tumor lesions and PVTT after pathological confirmation[7].

In subgroup analyses, we observed that HAIC-combined systemic therapy appeared to confer greater benefits in treating HCC patients with main portal vein invasion compared to those without PVTT, suggesting the potential complementary effect of HAIC to systemic therapies in addressing this challenging clinical issue[52]. However, a study by Fu *et al*[7] that all included patients with PVTT showed that HAIC-combined therapy was less effective in patients with VP4 (main trunk) than those with VP1 (distal branches) or VP2 (second-order branches). This finding suggested that even HAIC was added to the systemic regimens, too late tumor stage

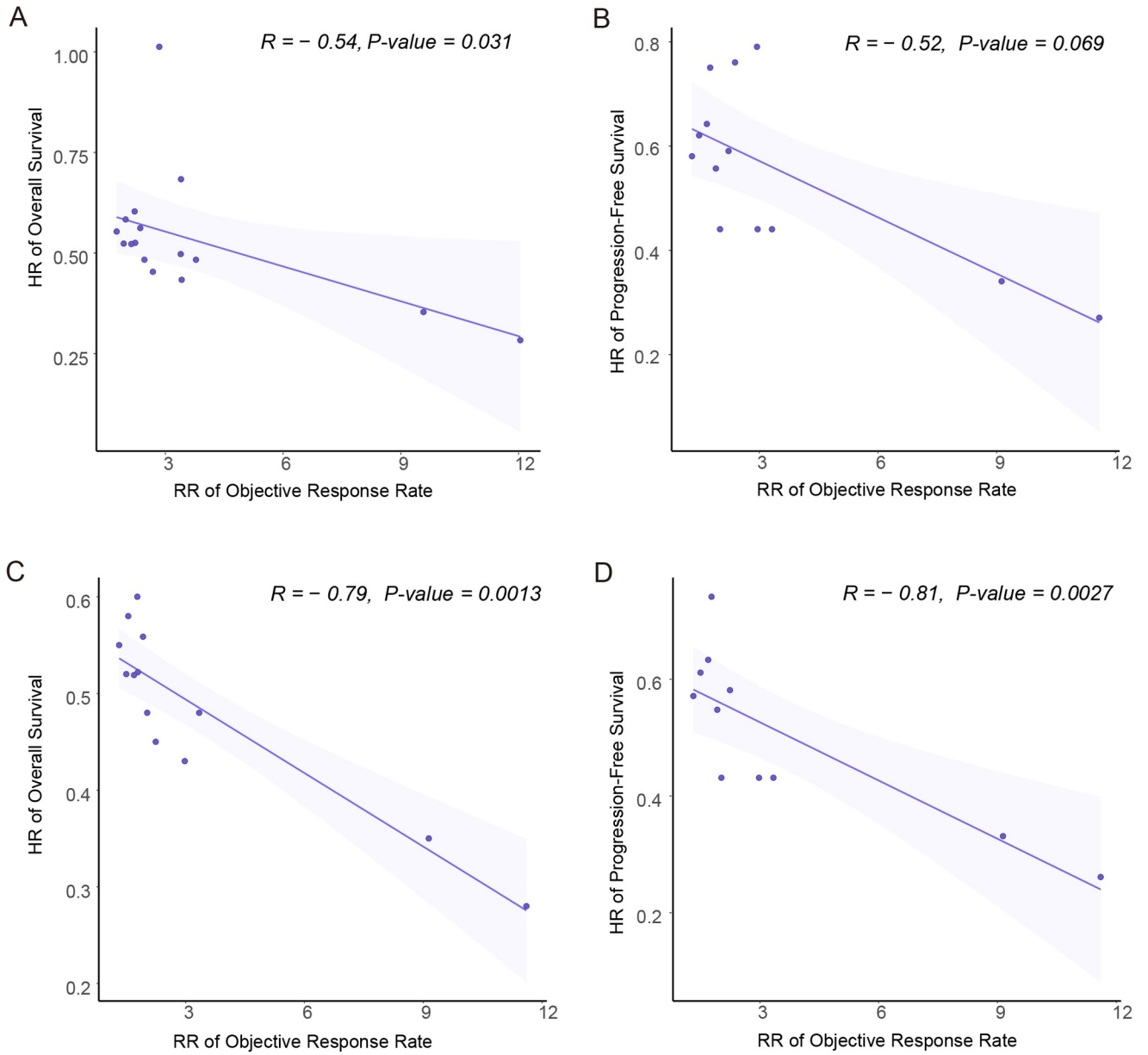

Figure 5. Correlations of objective response rates and survival outcomes. Each trial is represented by a dot. The purple line serves as an indication of linear relationship. R refers to coefficient of determination. *P*-value <0.05 is recognized as the presence of statistical difference for association. A downward trend indicates longer OS/PFS. (A) Correlation analysis between ORR and OS in the overall population. (B) Correlation analysis between ORR and PFS in the overall population. (C) Correlation analysis between ORR and OS in patients accepting HAIC with FOLFOX regimens. (D) Correlation analysis between ORR and PFS in patients accepting HAIC with FOLFOX regimens.

remained a substantial obstruction for improved survival outcomes[7,53,54]. Furthermore, the results indicated that patients without PVTT did not benefit from integrated HAIC, and there was a scarcity of studies focusing on the efficacy of it for subgroups of these individuals, such as those with extrahepatic metastasis. The urgent requirement for prospective trials targeting PVTT-negative populations, such as those with advanced metastatic profiles, may uncover novel indications for HAIC integration. Moreover, in patients with solitary tumor, additional HAIC with systemic therapy achieved a better HR than those with multiple lesions, reflecting its highly selective role[6]. Similarly, in Guan *et al.*'s [12] study of all patients with extrahepatic metastasis, the ORR of distant metastatic sites was significantly lower than that of intrahepatic lesions, reinforcing its localized efficacy, implying that more powerful therapeutic combinations should be applied in this patient group. Besides, elevated AFP levels in HCC have been demonstrated as a potential indicator of more aggressive and advanced disease[55], which may account for being a risk factor for PFS. Our analysis further revealed that patients with impaired liver function or poor performance status derived reduced clinical benefit compared to those with preserved hepatic function and favorable baseline characteristics. It was not unexpected that patients with better general

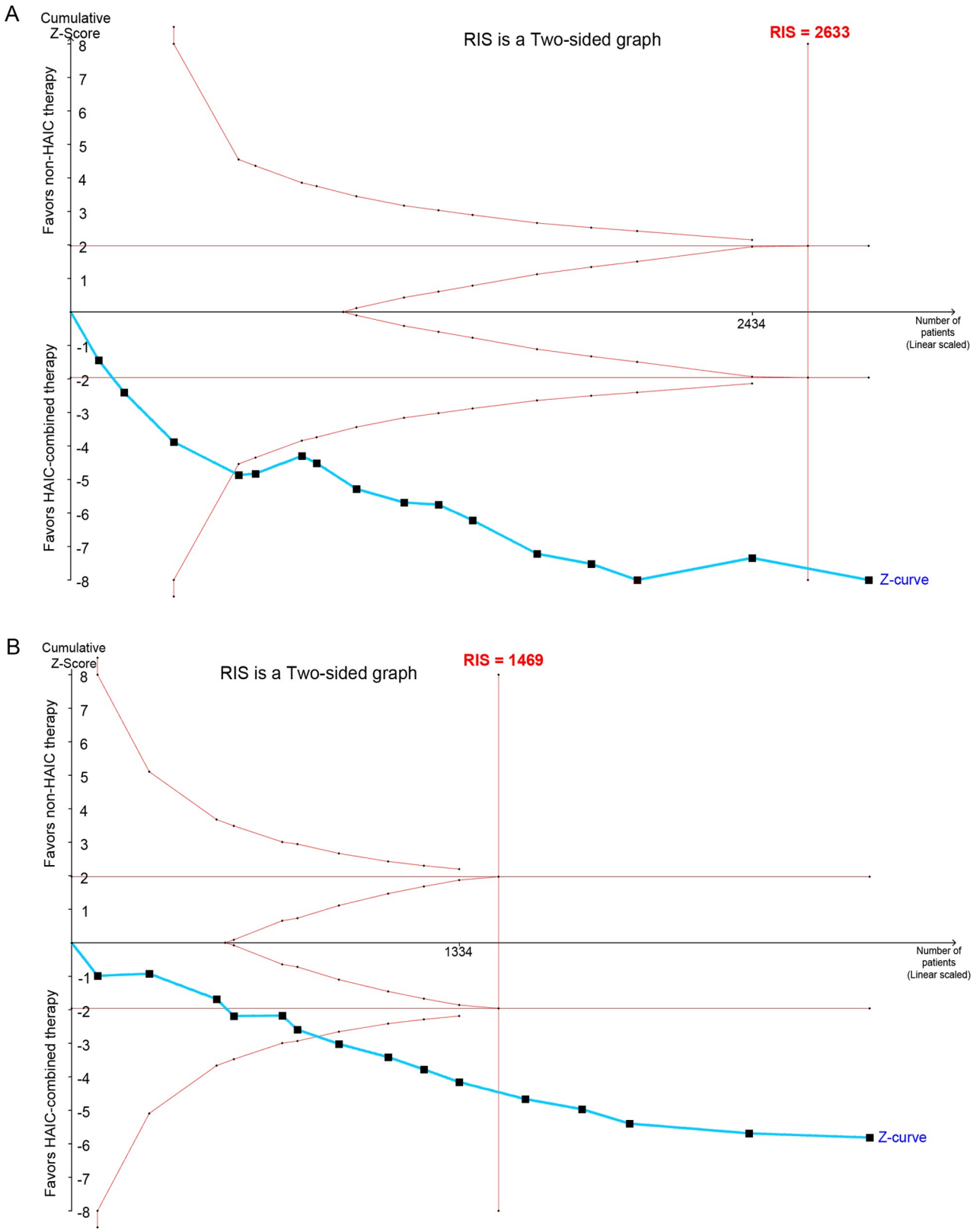

Figure 6. Trial sequential analysis of sixteen trials for objective response rate (ORR) and fifteen trials for disease control rate (DCR). The cumulative *Z* curve intersected both the conventional and the trial sequential monitoring boundaries, and surpassed the required information size (RIS). (A) for ORR, a random effect model was applied to build the cumulative *Z* curve (blue), the required information size of 2633 patients were calculated by using a relative risk reduction (RRR) of 30%. (B) for DCR, a random effect model was applied to form the cumulative *Z* curve (blue), the required information size of 1469 patients were calculated by using a relative risk reduction (RRR) of 15%.

conditions can not only yield superior quality of life, but tend to tolerate more treatment cycles and lower the incidence of treatment interruption or dose reduction, thus improving the possibility of successful conversion. Additionally, patients with significant hepatic fibrosis may exhibit diminished efficacy and compromised safety of integrated HAIC. This phenomenon can be attributed to several mechanisms. First, progressive fibrosis induces vascular architectural remodeling, culminating in reduced hepatic artery perfusion[56]. Consequently, chemotherapeutic agents delivered via HAIC may not reach adequate intratumoral concentrations, thereby attenuating the anticipated therapeutic response. Second, patients with high fibrotic burden are inevitably accompanied by limited functional hepatic reserve, demonstrating reduced tolerance to additional HAIC[57], as evidenced by our results of the higher incidence of grade 3–5 AEs. Notably, while our pooled analysis demonstrated comparable OS benefits between HBV-positive and HBV-negative subgroups, the clinical utility of HAIC in patients with high fibrotic burden remains uncertain. Therefore, quantitative fibrosis assessment through transient elastography or MR-proton density fat fraction should be incorporated in future integrated HAIC trials[58]. Patients with advanced fibrosis may benefit more from systemic therapies combined with antifibrotic agents rather than intensified locoregional approaches. In total, the findings of subgroup and prognostic factor analysis not only aligned with prior studies, but more importantly, provided valuable insights for future precise treatment[7,12].

Moreover, in subgroup analyses stratified by study characteristics that demonstrated statistical differences in meta-regression analyses, we observed that the platinum agent had a significant impact on OS and PFS. Furthermore, PFS in the oxaliplatin group was significantly higher than that in the cisplatin group when combined with TKIs. According to the pooled OS and DCR, cisplatin that killed tumor cells by the DNA-damage response[41], yielded no notable effect compared to TKIs alone when integrated with TKIs. Thus, we speculated that due to the distinct mechanisms of these two agents, HAIC regimens based on oxaliplatin might be preferable for combination with systemic therapies. Additionally, despite the type of systemic therapy being recognized as a potential source of heterogeneity, no notable distinctions were observed in OS, PFS, ORR, and DCR between studies using TKIs alone versus TKIs plus ICIs, implying that HAIC may offer a robust synergistic effect for systemic therapy regardless of specific systemic regimens. Nevertheless, more solid evidence is urgently required to identify the potential factors and mechanisms to find optimal strategies for the integration of HAIC treatment. The study design also notably affected the PFS and ORR. The ORR of RCTs was significantly better than that in retrospective cohorts, but patients receiving HAIC-integrated treatment consistently showed more favorable outcomes compared to those without HAIC in both study types. These results suggest that the pooled outcomes were not substantially influenced by the inherent biases of retrospective studies, thereby supporting the validity of future RCTs.

For the treatment-related AEs, the incidence of grade ≥3 AEs was significantly higher in HAIC-combined group than in non-HAIC group. Pooled analyses showed that HAIC group exhibited higher frequencies of elevated AST, elevated ALT as well as decreased leukocyte, decreased platelet, attributed to platinum drug-induced liver toxicity and myelosuppression[12,59]. These toxicities were reported to be reversible between two cycles of HAIC treatment with corresponding supporting medications reported by previous studies[12,26]. In addition, the higher incidence of abdominal pain during oxaliplatin infusion could be relieved through spasm relief drugs or slowing the infusion of oxaliplatin[12,27]. Furthermore, the increased frequency of gastrointestinal events, such as nausea, vomiting, and diarrhea may result from chemotherapy, particularly for drug diversion to the gastrointestinal tract or cholecyst[28], which could be resolved through gastroduodenal artery embolization during HAIC[28]. Overall, treatment-related AEs in both groups were manageable through dose modification, temporary treatment discontinuation as well as targeted interventions, supporting the conclusion that HAIC-based regimens are safe and tolerable in clinical practice. As is well-established, patients treated at high-volume HAIC centers demonstrate superior clinical outcomes, which are attributable to standardized perioperative management protocols. Our analysis revealed two critical findings. First, we observed that most treatment centers in the included studies were capable of undertaking the high-volume interventional procedures. The median number of patients receiving integrated HAIC was 89, with 13 studies enrolling ≥50 patients. Second, comparable survival outcomes were observed between high-volume (≥89 patients) and low-volume (<89 patients) subgroups, confirming the stability of our pooled estimates. Nevertheless, these findings underscore the necessity for multidisciplinary evaluations to optimize patient selection and protocol-driven AE mitigation, particularly given the higher incidence of grade ≥3 toxicities with combination HAIC-systemic therapy[60].

It is noteworthy that several advantages in our study. First, we investigated the efficacy and safety of integrated HAIC for systemic therapy including TKIs and TKIs plus ICIs, providing preliminary evidence for future clinical practice. This approach is likely to set a new benchmark for advanced HCC. Second, we conducted detailed meta-regression and subgroup analysis, providing a reference to select beneficial populations. Thirdly, prognostic factor analyses were performed to identify risk and protective factors. Both of them contributed to future individualized treatment. Fourthly, we observed that HAIC plus systemic therapy could convert high tumor response into survival benefit and supported ORR as a potential surrogate endpoint. Finally, the TSA indicated the stability of the conclusion.

Several limitations should be interpreted. First, moderate heterogeneity existed in our pooled results. Hence, we have conducted comprehensive analyses, including meta-regression analysis, subgroup analysis, and sensitivity analysis to identify its potential sources. Second, evidence from RCTs was still lacking, which may result in bias from selection and performance. Third, the exploration of extra HAIC approaches is mainly conducted in Asia, and conclusions need to be validated globally. Fourthly, several information conducive to precision treatment, including predictive tumor markers, were not feasible among the included studies[41,43]. Finally, due to insufficient data, we failed to explore the optimal combination regimen and detailed implementation.

Conclusion

Integrating HAIC to systemic therapy could bring favorable survival benefits for advanced HCC, and the toxicity was manageable. The combination of HAIC plus TKIs and/or ICIs has the potential to establish a new benchmark of survival in

advanced HCC. Further high-quality researches are necessary to standardize the integration of HAIC into systemic regimens and to refine combination strategies.

Ethical approval

Not applicable.

Consent

Not applicable.

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Author contributions

Study design and manuscript writing: D.L., H.L.; data collection and analysis: D.L., H.L., P.S., J.T., K.J., Q.C.; result discussion: D.L., H.L., P.S., J.T., Y.W., J.J., Q.H., S.P., D.Z., Z.D., D.W., T. L.; methodology, conceptualization, software, review and editing, supervision, project administration, funding acquisition: D. W., T.L. All authors read and approved the final manuscript.

Conflicts of interest disclosure

Not applicable.

Research registration unique identifying number (UIN)

Not applicable.

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Provenance and peer review

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Data availability statement

Not applicable.

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